

DATE: December 17, 1976

To : File

FROM : Joshua Lederberg

SUBJECT: Meeting on December 16th with Robert Owens, Fred Deserres from the NIEHS in re an EHS Center Application.

I began by giving them the history of my own interest in environmental health which stems to the beginnings of my career in medicine, its intercession by getting into more basic microbial genetics, my efforts to relate to medical school at Wisconsin, my expectations at Stanford and my feeling that basic science has its most important contribution to make in the preventive area. I showed them my 1969 letter and told them that I decided at that time not to subvert my laboratory efforts by taking on the organizational responsibilities that would be entailed by following through on the proposals about environmental health.

I then outlined the program that I had formulated rather roughly some months ago and completed during the last few days: the emphasis on (a) the metabolism of carbon; (b) specificity in chemical mutagenesis and (c) cost risk benefit studies. However, as elaborated here, I put the emphasis on closer analyses of the costs of mutation (against the views of Jack Shell who appeared to be totally nihilistic) rather than on the broader issues of extrapolation from animal data to toxicological risk and the health benefits of ameliorating them.

Then I reviewed the resources that were available to the department and constituted its milieu including the DENDRAL and SUMEX projects, the Human Biology Program, some of the organizational setup at Stanford that required a new direction.

I was reassured that the general framework that I was outlining was a very good match to the relevancy concerns of the institute. The risk estimation was perhaps their highest priority. Deserres was, of course, very much turned on by the mutagenesis study. I think they found Dennis quite an attractive person, but they felt I would have to work the hardest to establish the relevance and even more the feasibility of what he had in mind. The problems that we would be going into would appear to be immense for a program of our small scale.

The main message in terms of core support was to move as much as possible into the salary categories, so as to enable the funds thereby released from other sources to be used for the expansion of research programs.

In writing up the application I would have to give a broad description of current research and a more detailed account of what the core research efforts would be. Only a small amount of the total, perhaps 10%, should be reserved for discretionary fund.

A February 1 deadline does not seem feasible, and so we are talking now about June 1 and it would be December before there would be any chance of payment. This suggests that it would be a very good idea now to go to the Mellon Foundation and to see whether they could find funds on a shorter term to help us get started and commit some people.

Some miscellaneous notes. The cell sorter might be quite apropos. Some of the work that is now going on at the University of Washington in looking for somatic mutations. I should check with Arno Motulsky about that.

Fred's own main preoccupation is the accumulation of detriment from semi-dominant mutations of small effect, e.g. on I.Q.

He is also concerned that many of the assay systems do not pick up chromosome deletions and rearrangements. I told him about Ron Harris's work in this regard and raised the question whether aminopterin is capable of inducing or permitting deletions or is merely selecting for them.

There is also the old matter of whether highly radiation-resistant bacteria may not have mechanisms for double-strand DNA repair that are absent in most other organisms. If this is the case, then they might also be good vehicles for DNA splicing in vivo. He suggested ethylene dibromide as an excellent deletion producer, and he said he would send me ^{the} protocol. He also mentioned that hycanthone gave as much as 95% deletions compared to point mutations. Training is the subject of separate grants. They have not been able to get national research service predoctoral fellowships as yet but may in the future. So, we had better stick to our present programs for that. They do have a postdoctoral program and I should keep Carl Djerassi informed of this right away since it may well relate to their environmental toxicology program.

Our analytical studies probably relate most closely to what's going on at Oak Ridge in the search for pollutant mutagens. I should get Dennis to look further into this.

His studies may offer the most problems of validation since there is not that much of a _____ as far as they are aware on Dennis Smith. I should send them his c.v. We have to clarify exactly what we intend to do and what we do not intend to do unless we are prepared to go into them, for example going into the human. But perhaps I should go to Gene Robin about that. I wonder if David Sachs would have a role?

David Hoel has been in charge of workshops on risk estimates. He is the chief of the biometry division, and I should request proceedings on these workshops from him.

Deserres told me the sad story that his secretary quite gratuitously threw out all of his correspondence dated before 1974. As he himself is much interested in the history of the treatment of environmental mutagenesis, he was quite furious. Fortunately the records of the society were kept separately from his own correspondence and he still has that. I cautioned him that this would be the most interesting historical study. I should again send him copies of the Muller correspondence but perhaps wait until I have heard from the Lilly library.

I asked about the Nelson report and they will send me a copy in January which should be shared with the IOM subcommittee on preventive health.

In writing up the project I should indicate exactly what core support will do and this is of course the development of a cadre of principal investigators who will then be in a position to take a more autonomous role. I was quite straight about that with them. However, it is possible that I should ask Gan to take on the job of supervising the controlled mutagenesis study rather than try to get a new person in that particular area. Releasing part of his salary would help among other things in replacing the RCDA source of support that we had before.

This leaves me now with the dilemma what to do with my present research grant. Whether to stick to the transformation study or whether to try to justify going into the new work on controlled mutagenesis.

There will be a workshop in New Orleans at the end of January on every aspect of organic particulates, and I asked Fred to see about inviting Dennis Smith to attend.

I had called Alain Enthoven yesterday and found that he was really not too keen to diversify too much more from what he is in right now. This does not preclude some other form of collaboration with the bureau.

The lambda system that I have in mind comes out as being possibly the best answer to the question of a plasmid in which one could routinely select for lost mutations. It's funny that lambda 2 should end up as a candidate after all these years. Reading back that old paper it was fun to see how many perplexities were noticed at the time: for example that lambda 2 did not automatically take over a culture; and that we now understand reasonably well.

Well, now I have to see whether Dennis can be captivated by the same enthusiasm.